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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/071,174	REED ET AL.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-9,11-15,17-23,25-28,76,77 and 152-163* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *17-23 and 25* is/are allowed.

6)☒ Claim(s) *11,15,76 and 162* is/are rejected.

7)☒ Claim(s) *1,4-9,11-14,26-28,77 and 152-163* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

After further consideration, the amendment filed 5/19/2007 is now entered.

Claims 1, 4-9, 11-15, 17-23, 25-28, 76-77, 152-163 are currently pending and are examined herein.

Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claim Objections

1. Claims 5-9 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 5-9 are drawn to the isolated or recombinant nucleic acid of claims 1 wherein the sequence is less than a specific size. However, claim 1 only recites one "sequence", that "sequence" being the "polynucleotide sequence that is 95% or more identical to SEQ ID NO: 1". Since SEQ ID NO: 1 is 887 nucleotides in length, the longest possible length of the "sequence" of claim 1 (i.e., the polynucleotide sequence that is 95% or more identical to SEQ D NO: 1) is about 934 bases. Therefore, claims 5-9 do not further limit claim 1 as the "sequence" of claim 1 must already be less than 2.5kb (2500 bases).

Claims 1, 4-9, 11-14, 26-28, 152-163 are objected to because of the following informalities: claim 1 reads on an isolated or recombinant nucleic acid comprising a polynucleotide sequence that is 95% or more identical to SEQ ID NO:I, wherein said nucleic acid encodes a polypeptide that is an apoptosis inhibitor. Changing the phrase "wherein said

nucleic acid encodes a polypeptide that is an apoptosis inhibitor" to "wherein said polynucleotide sequence encodes a polypeptide that is an apoptosis inhibitor" would make it clear that it is the polynucleotide sequence, and not another part of the nucleic acid that encodes a polypeptide that is an apoptosis inhibitor. Claims 4-9, 11-14, 152-163 are also objected to as they depend on claim 1.

2. Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 11 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 11 specifically reads on the isolated or recombinant nucleic acid of claim 1 wherein the sequence is a nucleic acid sequence complementary to SEQ ID NO: 1 or SEQ ID NO: 1 wherein one or more T's are U (see part (c)). However, claim 1 specifically indicates that the "sequence" is a polynucleotide sequence that is 95% or more identical to SEQ ID NO: 1 and wherein the sequence encodes a polypeptide that is an apoptosis inhibitor. The specification does not appear to disclose any nucleic acid sequences which are complementary to SEQ ID NO: 1 or SEQ ID

NO: 1 wherein one or more T's are U and which also are 95% or more identical to SEQ ID NO: 1 and wherein the sequence encodes a polypeptide that is an apoptosis inhibitor. Furthermore, no such nucleic acid sequences can be envisaged.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the specification does not appear to disclose any of the indicated complimentary nucleic acid sequences, nor can any be envisaged.

Claim 15 is also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 15 is drawn to an isolated nucleic acid that hybridizes to the sequence set forth as SEQ ID NO: 1 under stringent hybridization conditions, wherein the sequence that hybridizes is the entire length of SEQ ID NO: 1. Here, claim 15 encompasses a genus of molecules that have a particular size (the entire length of SEQ ID NO: 1) and which hybridizes to SEQ ID NO: 1 under stringent hybridization conditions. Importantly, the isolated nucleic acid of is not required to have any particular sequence, thus there is no "core structure" common to the nucleic acids encompassed by the claims.

As indicated above, to provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. In this case, the specification does not provide sufficient distinguishing identifying characteristics of the genus of nucleic acid sequences.

Claim 76 is also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 76 encompasses a method that utilizes a nucleic acid that encodes a polypeptide that is 90% identical to SEQ ID NO: 2, wherein the nucleic acid sequence is greater than 70 bases pairs in length and encodes a polypeptide that inhibits apoptosis. Therefore, the claims encompass a genus of different nucleic acid sequences.

As indicated above, to provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the specification does not disclose an adequate description of the structural elements that are required for producing a polypeptide as indicated in the claim which is an inhibitor of apoptosis. In other words, the specification does not indicate which sequences are critical for the required function, thus the required structure/function relationship has not been

described. The only sequences that meet have been adequately described are: SEQ ID NO: 1 and the nucleic acid sequence which encodes the polypeptide of SEQ ID NO: 2. Furthermore, the guidelines for examination indicate that nucleic acid sequences that are 95% identical to a specific sequence and which have a specific function may also be described. Accordingly, the nucleic acid sequence that is 95% identical to SEQ ID NO: 1 and which encodes a polypeptide that is an inhibitor of apoptosis is also acceptable. Limiting the genus of nucleic acid sequences to any of these specific sequences would obviate this rejection.

Applicant is respectfully reminded that *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states, "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). Here, the skilled artisan cannot envision the detailed chemical structure of the genus of nucleic acid molecules encompassed by the claims. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Additionally, Claims 76 and 162 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for producing a polypeptide in solution or in vitro, does not reasonably provide enablement for a method of producing a polypeptide in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

> *Wands* states on page 1404,
> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims encompass making a polypeptide in vivo and encompasses making the polypeptide as a therapeutic polypeptide in vivo, which encompasses gene therapy. As such, the invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The instant claims are broad in the sense that the claims merely recite a method of producing a polypeptide comprising expressing a nucleic acid encoding an amino acid sequence. Although the claims do not explicitly indicate that the polypeptide is produced *in vivo,* it is noted that dependent claims 77 and 163 indicated that the polypeptide is produced in solution or in a cell *in vitro*. Since the independent claims must be broader than the dependent claims, claims 76 and 162 can properly be considered to encompass producing the polypeptide *in vivo.* Furthermore, given their broadest reasonable interpretation consistent with the specification, the claims encompass expressing the polypeptide in order to treat a disease.

The unpredictability of the art and the state of the prior art

The specification does not disclose that the methods have effectively treated any disease or disorder by administering a nucleic acid which encodes the protein and expressing the protein *in vivo* in order to obtain a therapeutic effect.

It is noted that the claims are not directed to the treatment of any particular disease; therefore, given the broadest reasonable interpretation, the claims encompass treating any disease or disorder.

At the time of filing, the relevant art considered gene therapy as a whole to be unpredictable. For instance, **Anderson** (Nature 1998; previously of record) teaches,

> *"The challenge is to develop gene therapy as an efficient and safe drug delivery system. The goal is more difficult to achieve than many investigators had predicted... The human body has spent many thousands of years learning to protect itself from the onslaught of environmental hazards, including the incorporation of foreign DNA into its genome. (See p. 25, second paragraph). The ultimate goal of gene therapy research is the development of vectors that can be injected, will target specific cells, will result in safe and efficient gene transfer into a high percentage of those cells, will insert themselves into appropriate regions of the genome (or will persist as stable episomes), will be regulated be either by*

administered agents or by the body's own physiological signals, will be cost effective and will cure disease. (See p. 30, first paragraph)."

Dang et al. (Clin. Cancer Res. 1999; previously of record) teaches "Although significant progress has been achieved in our understanding of the limitations of gene therapy by suboptimal vectors, host immunological responses to the vectors, and the lack of long term stable expression, the major challenge that limits clinical translation remains in achieving efficient gene delivery to target tissues" (page 474, col. 2, last paragraph).

With respect to using the claimed method for treating a disease, it is noted that the claims encompass treating any disease. Therefore, given the broadest reasonable interpretation consistent with the specification, the claimed method can be interpreted as treating any disease associated with an abnormally high level of apoptosis such as diabetes by administering a polynucleotide encoding the anti-apoptotic polypeptide to a diabetic patient.

However, regarding gene therapy for diabetes, **Levine** (Mol. Med. Today 1999; previously of record) indicates many of the obstacles that need to be overcome in order to create an effective gene therapy for diabetes including gene transfer problems, cell transfer problems, and the responsiveness of the transduced cells to blood glucose levels. Levine focuses on gene transfer into pancreatic beta cells.

Regarding gene transfer into beta cells, Levine indicates that there are two general means by which therapeutic genes can be introduced into beta cells: by transducing the islet cells ex vivo and reintroducing the cells into the pancreas of the subject (see p. 165, last paragraph), and transfer of the therapeutic gene(s) into pancreatic beta-cells in vivo. However, Levine also indicates, "Successful islet cell transplantation has proved to be an elusive goal... (and) to date,

there are no studies demonstrating that [in vivo gene transfer into beta-cells] can be done." (See p. 166).

Levine teaches that both type I and type II diabetes results in the apoptotic death of beta-cells (see p. 166-167) and further indicates that preventing beta-cell apoptosis may be potentially applicable to both type I and type II diabetes either by inhibiting apoptosis of beta cells before they die via gene transfer of anti-apoptotic genes such as Bcl-2 into the beta cells (e.g., see p. 168-169). However, gene transfer into beta cells is unpredictable as indicated above.

Furthermore, Levine also indicates that successful gene transfer into beta cells (either in vivo or ex vivo) and/or successful cell transplant are not the only obstacles to obstacle to overcome in order to effectively treat diabetes. Once the therapeutic gene(s) or cells are successfully delivered, the cells must be able to respond changes in blood glucose levels:

> *"A definitive treatment for diabetes mellitus will be one that maintains a normal blood glucose concentration in the face of fluctuating dietary intake. To accomplish this there must be mechanisms to sense the amount of blood glucose coupled to rapid release of the right amount of insulin."* (See p. 165, abstract).

Levine summarizes the state of gene therapy for diabetes by stating, "the ultimate goal of a definitive, permanent treatment of diabetes through gene therapy lies in the distant future." (p. 170, last paragraph).

In view of the teachings of Anderson, Deng and Levine, it is clear that gene therapy methods are unpredictable in nature. Furthermore, the specification does not disclose working examples or provide guidance which would overcome the art-recognized problems. Therefore, additional experimentation would be required in order to practice the invention to the full scope encompassed by the claims.

Therefore, in view of the breadth of the claims, the limited amount of direction and/or guidance provided in the specification, as well as the art recognized unpredictability of gene therapy and the limited working examples, it is concluded that an undue amount of experimentation is required for one skilled in the art to make and use the claimed invention to the full scope encompassed by the claims.

Allowable Subject Matter

5. Claims 17-23 and 25 are allowed.

6. Claim 77 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Monday-Thursday 8:00 a.m.-6:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. E. Angell/
Primary Examiner
Art Unit 1635